

Hydroxyurea

Hydroxyurea is indicated for the treatment of certain malignancies and sickle cell anemia, and has been used investigationally for the treatment of HIV. Its potential safety and effectiveness for treatment of HIV have not been established, and clinicians should be aware of important safety precautions regarding its use.

Hydroxyurea does not have direct antiretroviral activity; rather, it inhibits the cellular enzyme ribonucleotide reductase, resulting in reduced intracellular levels of deoxynucleoside triphosphates (dNTPs) that are necessary for DNA synthesis [1].

Hydroxyurea preferentially depletes intracellular dATP; therefore, antiretroviral activity and/or toxicity of adenosine analogues, such as ddI, may potentially be enhanced in combination with hydroxyurea.

Hydroxyurea also induces the activity of cellular kinases that phosphorylate nucleoside analogue reverse transcriptase inhibitors, potentially further enhancing their antiretroviral activity and/or toxicity.

There have been no data from controlled clinical trials that convincingly support the benefit of hydroxyurea as an adjunct in the treatment of HIV infection. In limited studies, the addition of hydroxyurea to a regimen of ddI + d4T or ddI alone appeared to result in moderately enhanced antiretroviral activity [2-4], although the optimal dosage and dosing schedule were not determined. In contrast, in ACTG 5025, a randomized, controlled clinical trial conducted in subjects on potent antiretroviral therapy with levels of plasma viremia <200 copies/mL [5], no statistically significant differences in viral load suppression were observed in patients receiving hydroxyurea 600 mg twice daily in combination with ddI + d4T + indinavir compared to those receiving the combination regimen without hydroxyurea. Additionally, a substantial decrease in median CD4⁺ T cell count was observed in the hydroxyurea treatment group. Observations of blunted or reduced CD4 responses were also reported by other investigators [6-8]. Importantly, the ACTG 5025 trial was prematurely terminated due to higher rates of drug toxicity in patients randomized to the hydroxyurea-containing arm. Among 68 patients randomized to hydroxyurea, three deaths related to complications of pancreatitis were reported. The increased frequency of fatal pancreatitis in the hydroxyurea-containing arm was not statistically significant and had not been reported previously. These cases of fatal pancreatitis do, however, raise the question of whether hydroxyurea in combination with ddI + d4T may increase the risk of ddI-associated pancreatitis.

Additional concerns regarding the use of hydroxyurea in HIV infection have been raised in this trial and other studies, and include an increased risk of persistent cytopenias [9] and hepatotoxicity [10], the drug's teratogenic properties (FDA Pregnancy Category D), and an increased risk of neuropathy [11, 12].

In summary, the current clinical trial data have not demonstrated virological and immunological benefit of hydroxyurea as adjunctive therapy to antiretroviral regimens when compared to antiretroviral therapy alone, and hydroxyurea should generally not be offered. (DII) Clinicians considering the use of hydroxyurea in a treatment regimen for HIV should be aware of the limited and conflicting nature of data in support of its efficacy, and the importance of monitoring patients closely for potentially serious toxicity.

References

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